Review article

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Brain growth, fetal malnutrition, and clinical consequences[1] [2]

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1 Introduction

Fetal malnutrition resulting in growth retardation has been identified as one major risk factor for perinatal mortality and morbidity [3, 20, 63, 97, 104]. The significance of the problem results from the incidence of about one third SGA infants among all low-birth-weight infants [8, 39, 90]; the definition of low-birth-weight has been slightly altered from a birthweight of '2500 g or less' to 'less than 2500 g' regardless of the duration of the gestation [40]. In the Groningen Perinatal Project [62] 13.2 per cent of all newborn infants were growth retarded, and the neonatal neurological morbidity was highest in the group with intrauterine growth retardation.

Before the introduction of intensive prenatal and postnatal care, as well as of early and high-caloric feeding of infants with intrauterine growth retardation, their development has been reported frequently to be less favorable than that of infants with appropriate intrauterine growth (AGA) [8, 46, 59, 87, 98]. Only recently it has been stressed by HAGBERG et al. [52] that fetal malnutrition plays an important role in the pathogenesis of cerebral palsy syndromes and mental retardation today – quantitatively unchanged from 1954 to 1970 – in Sweden.

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Curriculum vitae

INGEBORG BRANDT, *born in Berlin in 1931, recieved her Dr. med. degree from the Freie Universität in 1955, after studies in Berlin and Tübingen. After postgraduate training in pathology in Berlin, she specialized in pediatrics at the Children's Hospital for Rheumatic Diseases in Garmisch-Partenkirchen and Children's Hospital Berlin-Charlottenburg. She belongs to the Bonn University Children's Hospital ever since 1965, interrupted only by several stays abroad.*
In 1966–67, she recieved further training in Paris at the International Children's Center and also in London, where she worked with Professor J. M. TANNER *at the London Institute of Child Health. This was followed by a visit to major child development centers in the U.S.A., as for example Berkeley, Denver, Boston, New York. From 1967 onwards, she has been engaged in a continuing multidisciplinary longitudinal study of growth and development in appropriate and small for gestational age preterm and full term infants from birth to age six. She is currently working on an overall evaluation of the long-range results for neurological, motor and mental development.*

Infants with the intrauterine growth retardation syndrome or small for gestational age infants are defined as those with a birth weight below the 10th percentile of intrauterine growth standards. The 10th percentile of the widely used LUBCHENCO curves [71] – at least up to 38 postmenstrual weeks – agrees quite well with the

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corresponding curves of other authors [for example 15, 57, 60, and others quoted in 10]. The synonyms for these newborn infants in the literature are listed in Tab. I; among these the term SGA is most commonly used.

Tab. I. Intrauterine growth retardation syndrome, synonyms.

small-for-dates (SFD)	BUTLER and BONHAM [19]
chronic fetal distress	GRUENWALD [50]
small-for-gestational age (SGA)	LUBCHENCO et al. [72]
intrauterine malnutrition	SCOTT and USHER [90]
foetal growth retardation, intrauterine growth retardation (IUGR)	WIGGLESWORTH [101]
small-for-date infants	DRILLIEN [38]
light-for-dates	NELIGAN [79]
dysmaturity	DEWHORST et al. [33]
fetal malnutrition, undergrown in utero	MILLER and HASSNEIN [76]
fetal dystrophy	KLOOS and VOGEL [66]
foetal deprivation of supply (FDS)	HAGBERG et al. [52]

2 Relationship between head circumference growth and brain size

Growth in head circumference in normal infants is closely related to brain size in the last weeks of gestation and in the first year of life as has been shown in many studies [10, 14, 17].

Recently DOBBING and SANDS [36] published an approximate formula linking head circumference and brain weight:

$$g = \frac{x^3}{100} - \frac{3000}{2x} \quad \text{where } g = \text{brain weight in g and } x = \text{head circumference in cm}$$

This formula makes it possible to convert longitudinal head circumference data to estimated brain weights for the period between the ages of 28 postmenstrual weeks and two years [12].

2.1 Brain weight, distance

Fig. 1 demonstrates estimated brain weights from 29 postmenstrual weeks to 18 months after term in a computerplot, mean with one and two standard deviations, unsmoothed results. The high growth rate during the perinatal period, which is defined as the time between 28 postmenstrual weeks and the seventh day after term [80, 81] is evident. Between 32 and 39 weeks the brain doubles in weight from 183 g (SD 31) to 365 g (SD 40). During the first six months after term, brain weight is doubled again, i.e. from 392 g (SD 40) at term to 870 g (SD 70) at the age of six months (shaded area in Fig. 1). Thereafter growth slows considerably; at 18 months brain weight amounts to 1072 g (SD 96), an increase of only 33% over the value at six months [12].

A comparison of the calculated brain weight of AGA preterm infants from 30 to 40 postmenstrual weeks reveals a close correspondence with brain weight data from autopsies of normal infants reported by LARROCHE and MAUNOURY [67] as well as by GRUENWALD and MINH [49]. For example, at 38 weeks brain weight amounts to 339 g in all three groups (Tab. II).

Tab. II. Brain weight in grams, boys and girls.

	postmenstrual weeks					
	30	32	34	36	38	40
AGA preterm infants Bonn, mean	149	183	231	285	339	392
Autopsies, GRUENWALD and MINH [49], mean	166	209	246	288	339	380
Autopsies, LARROCHE and MAUNOURY [67], 50%	159	197	241	283	338	385

2.2 Brain weight, velocity

Fig. 2 demonstrates the growth velocity of the brain, calculated in grams per month from the distance data in Fig. 1. Before expected date of delivery there is a period of very rapid brain growth with a peak of 121 g to 124 g (SD 25) between the ages of 33.5 and 36.5 postmenstrual weeks. At 3.5 months after term the velocity has slowed to 50 per cent (64 g, SD 11) of its peak,

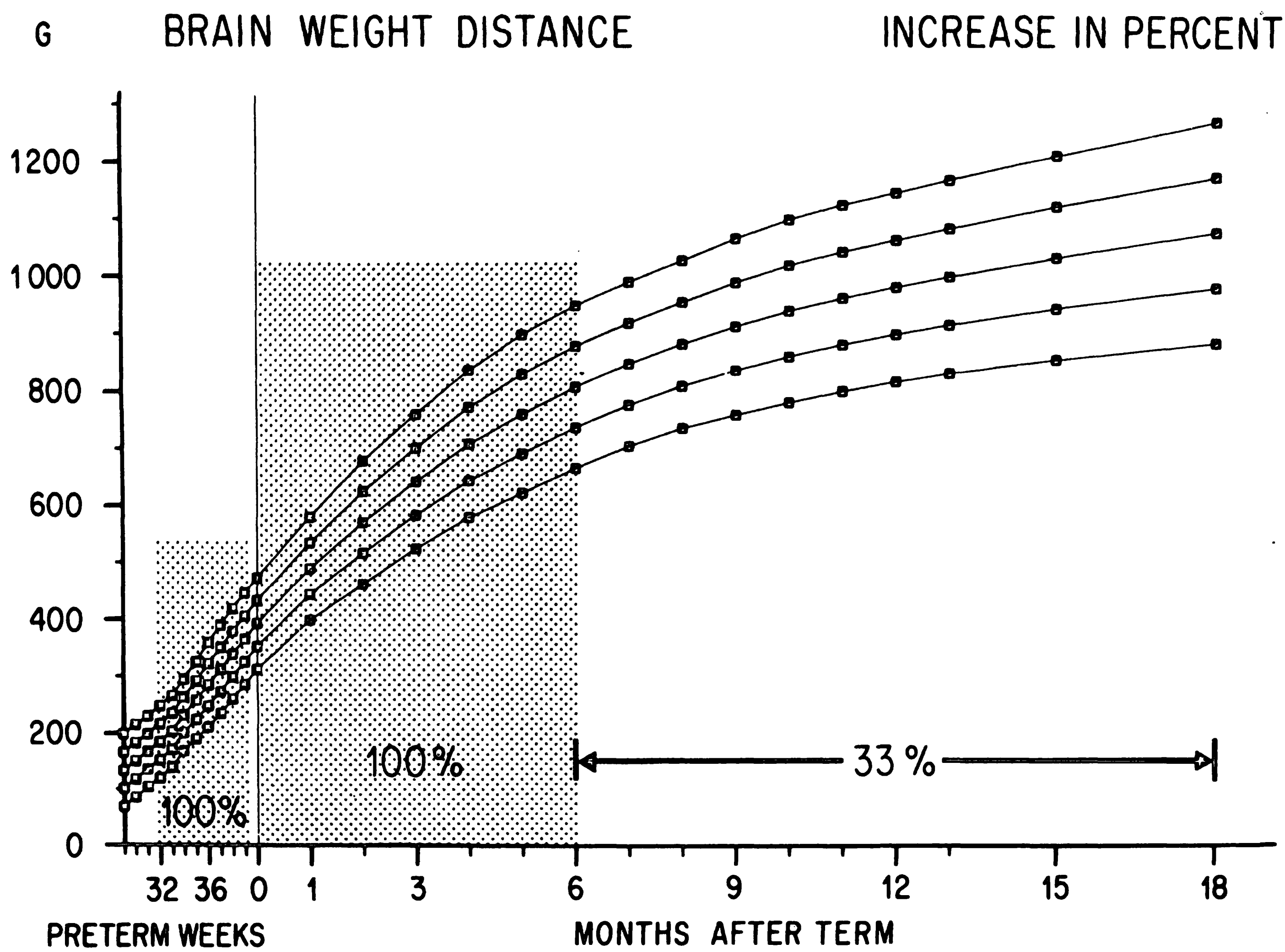


Fig. 1. Calculated brain weight (g) of AGA preterm infants (mean ± 1 and 2 SD).

at ten months to 20 per cent and at 19 months to only 10 per cent (12 g, SD 5).

If the end of the growth spurt period is arbitrarily defined as a velocity decrease to 10 per cent of its mean peak, then this results in a duration up to 19 months after term for the brain. According to DOBBING [37] the brain growth spurt 'ends between the second and third birthday'.

3 Morphogenesis during the brain growth spurt

When the brain growth spurt begins – about the middle of gestation – the adult number of neurons has already been largely achieved [34, 35, 37]. There are only the late-dividing granular neurons of the cerebellum which impinge on the spurt period [37], being the only ones which could be numerically affected by intrauterine malnutrition. Possibly this may have consequences for motor coordination and may be responsible for the "clumsy child".

The brain growth spurt consists of glial multiplication, myelination, dendritic growth with development of the dendritic tree, and establishment of synaptic connections [35, 37].

Myelination: Myelin accounts for a large percentage of brain weight (greater than 25%) and accumulates over a relatively short period. Only a small fraction is present at birth. Over 50 per cent cerebrosid-sulphatide, used by CHASE [24] as an index of myelination, accumulates between ages 12 and 24 months and formation is probably complete prior to the age of four years.

An example of the cycles of myelination in man from five fetal months to three years is shown

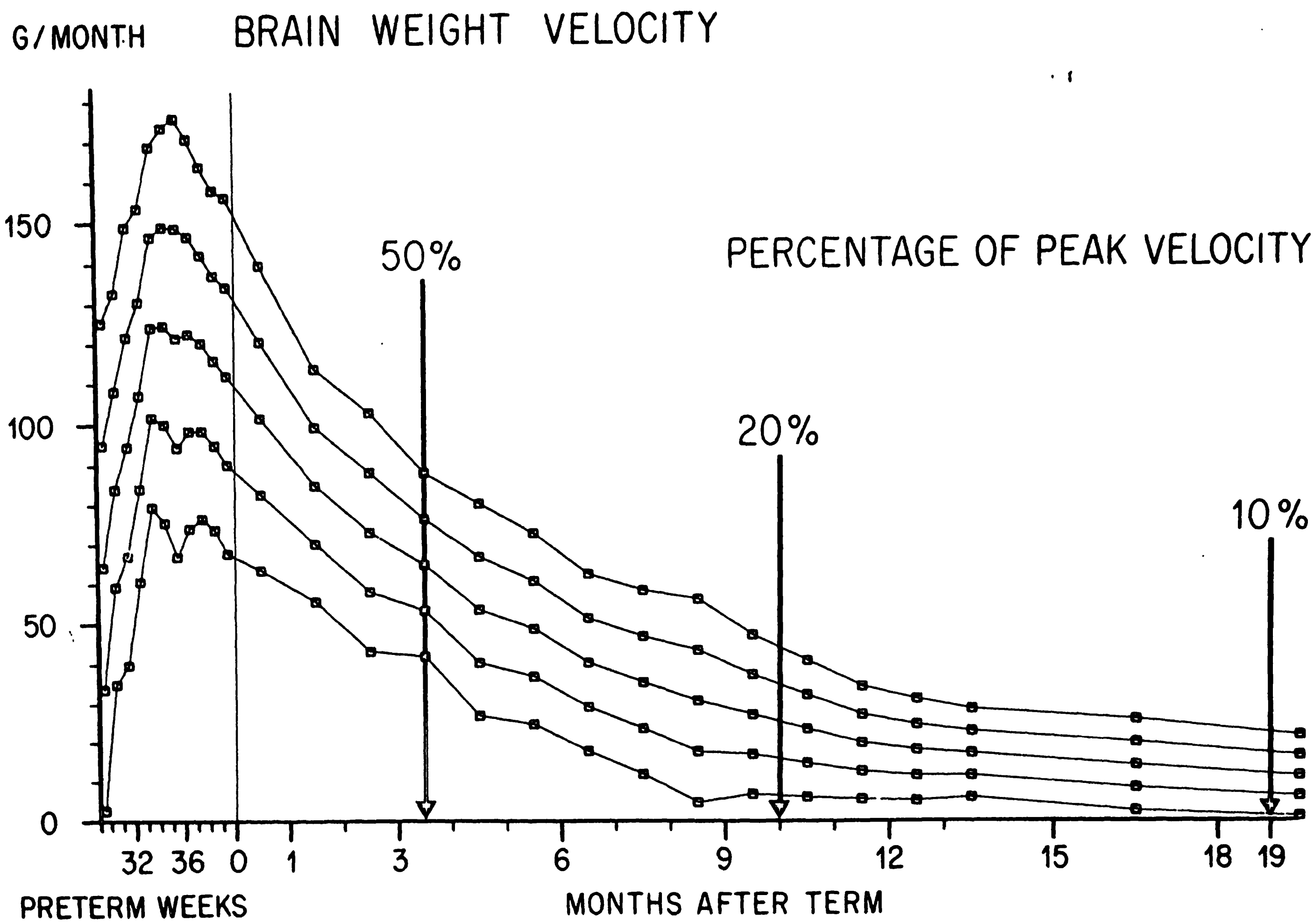


Fig. 2. Calculated brain weight velocity (g/month) of AGA preterm infants (mean ± 1 and 2 SD).

in Fig. 3 [from YAKOVLEV and LECOURS, 103]. The width and length of bars indicate progression in the intensity of staining and density of myelinated fibres; the vertical stripes at the end of bars indicate approximate age-range of termination of myelination estimated from comparison of the foetal and postnatal material with the material from adults in the third and later decades of life [103]. In the forebrain no myelinated fibres are encountered before the seventh fetal month. In the last trimester however there occurs an almost explosive spurt of myelination in the subthalamic region, field of Forel, thalamus and pallidum.

A comparison between the cortex lobulus paracentralis, region FA γ foot, of a preterm infant of 36 postmentrual weeks and a full term infant reveals a difference in thickness of 100 per cent in favor of the full term infant [82].

At about the middle of the ninth fetal month the fibres of the statoacoustic system complete already the cycle of myelination. From the sixth fetal month almost to term they dominate in myelin preparations the picture of the brain stem (Fig. 3, bar three).

Dendritic growth: An example for the dendritic arborization is shown in Fig. 4. Here are compared pyramidal neurons (camera lucida drawings from GOLGI-COX preparations) of the motor cortex in the region of the hand (FA γ) in a newborn infant (left) with those of a six-month infant (right), CONEL [27, 28]. The dendrites and axons of all cells have increased in size, length, and compactness of structure during the six months' period. The growth of the dendrites seems to be particularly important for the postnatal development of psychomotor functions; these dendrites are the

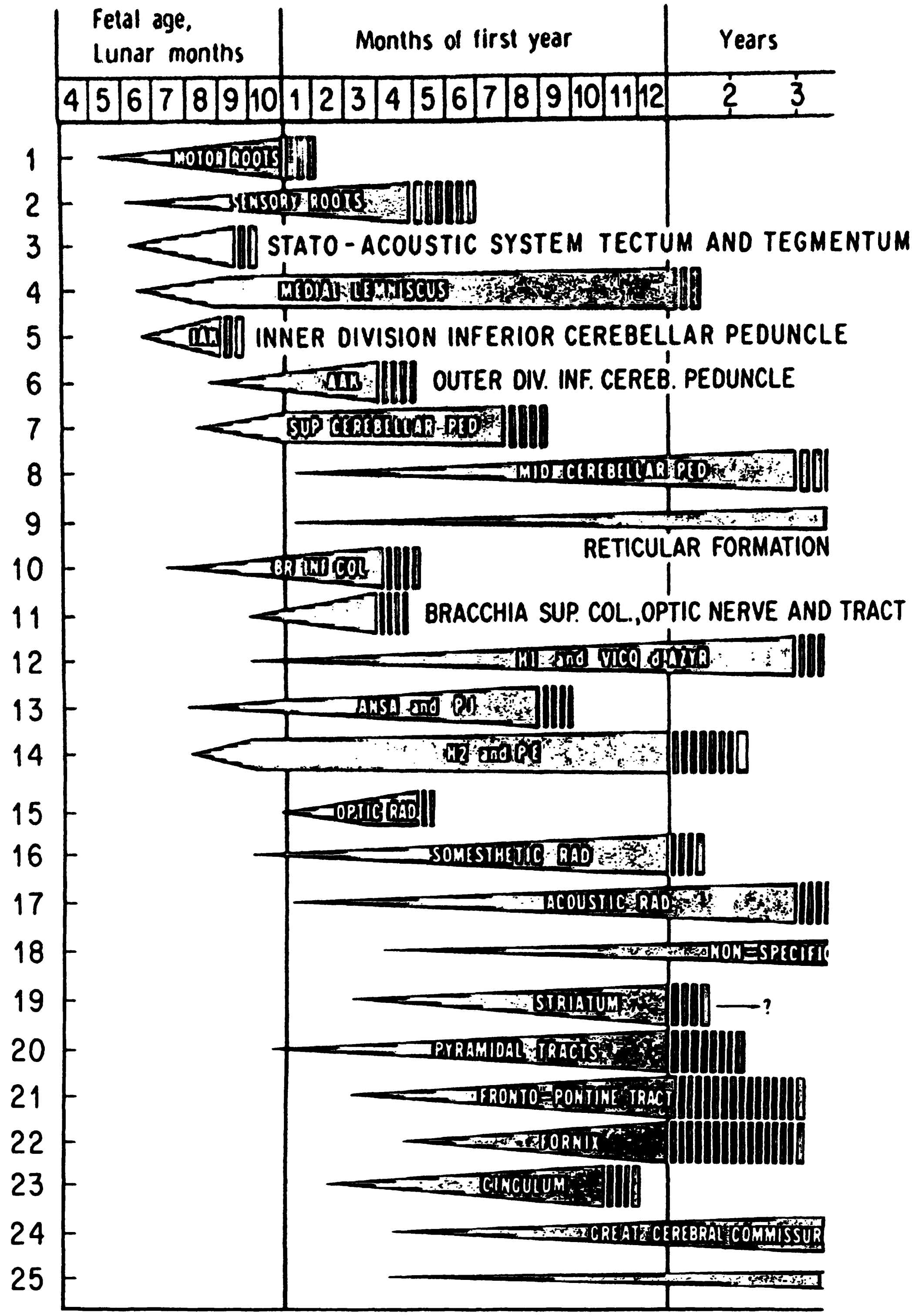


Fig. 3. Cycles of myelination. The width and length of the bars indicates progression in the intensity of staining and density of myelinated fibres; the vertical stripes at the end of bars indicate approximate age-range of termination of myelation [YAKOVLEV and LECOURS, 103].

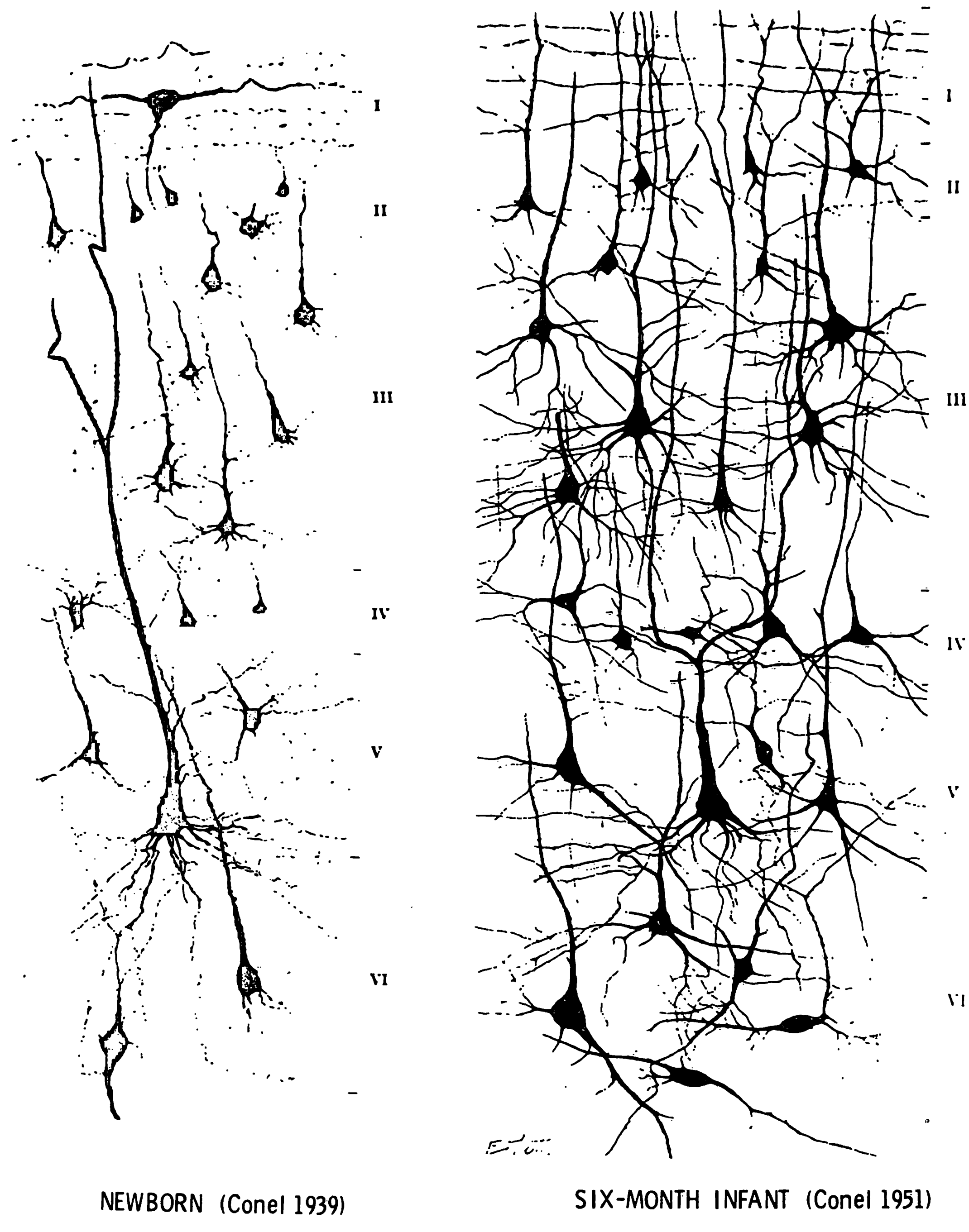


Fig. 4. Camera-lucida drawings from Golgi-Cox preparations of pyramidal neurons of the motor cortex in the region of the hand (FAγ) in a newborn infant (left) and in a six-month infant (right), CONEL [27, 28].

main location of synaptic connections between the neurons [42].

Synaptic connections: The experimental findings of HUTTENLOCHER [61] suggest that neurons in human frontal cortex acquire their full complement of synapses by age one year, and then some synaptic loss occurs subsequently. An example for the synaptic contacts in pyramidal neurons with their variations in structures and arrangements, and also the relationship of such contacts to different levels of the dendritic tree, as described by HAMLYN [53] in his electron microscope study is shown in Fig. 5.

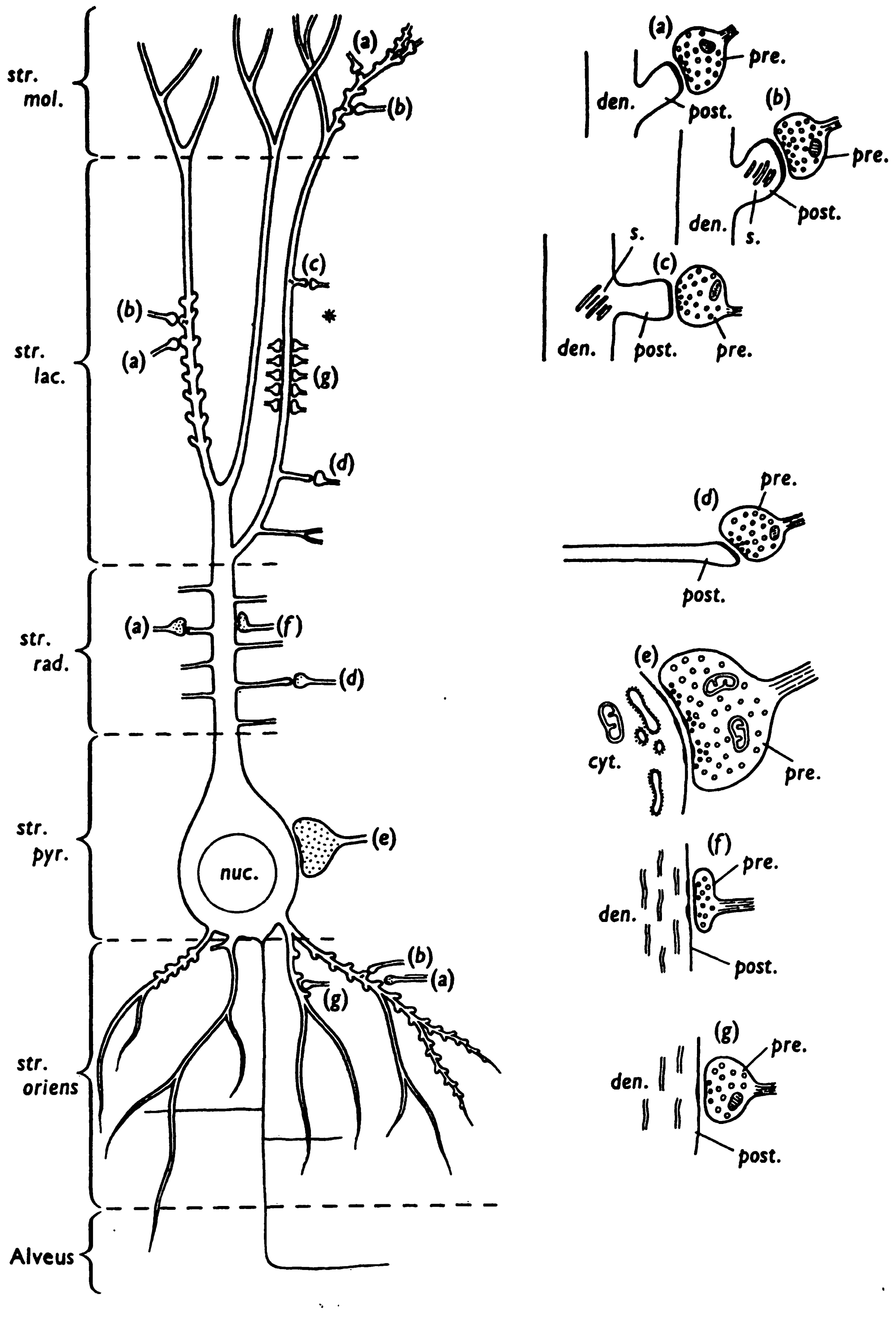


Fig. 5. Left: Drawing of a pyramidal neuron 'note to scale' from the Ammon's Horn, showing the variety of synaptic contacts, designated a–g, on the dendritic branch. Right: Details of these seven different types synapses. [Electron microscope study of HAMLYN, L. H., 53].

4. Consequences of fetal malnutrition

The belief that 'malnutrition spares the brain' is still surprisingly prevalent in our teaching today [37]. DOBBING [37] explains this by the fact that late 19th century examinations took place generally on the brain of fully adult people dying of extreme starvation. Whereas most of the tissues of the body were profoundly affected by starvation, the brain was found to be completely unaffected. So these conclusions were drawn from studies, based on adults only, at a time, when infants were considered merely miniature adults.

Contrary to that von BECHTEREW reports already in 1895 [5] a weight reduction of all organs including the brain, in starved newborn cats and dogs, and similar findings in human newborns, who died from hunger.

Only in the third quarter of the present century one arrived at the discovery that fetal and infant malnutrition may have consequences for the brain. Today it is proved in many studies that in infants with prenatal undernutrition not only weight and length are affected but also, though to a varying degree, head circumference, an acknowledged parameter for brain size [47, 58, 74]. LECHTIG et al. [69] for example, report from their carefully designed and carried out Guatemala longitudinal study that the newborns of undernourished mothers are retarded not only in weight but also in length and head circumference. The consequences of prenatal nutritional deprivation for the rapidly growing brain are dependent on the timing, duration and severity of the restriction.

As demonstrated in Fig. 6 where weight, head circumference and supine length after birth of 43 SGA preterm infants (circles) of the Bonn study [10] are plotted on the intrauterine growth curves of LUBCHENCO et al. [71, 72], the measurements are reduced in all three parameters with the weight most affected. The circles with an asterisk signify infants with postnatal catch-up growth of head circumference [8, 10]. The photograph in Fig. 6 below shows a boy, born by elective Cesarian section in the 35th postmenstrual week with a birth weight of 850 g as an example of extreme growth retardation. The birth measurements (encircled in Fig. 6) are clearly reduced with the head least affected. In those infants with follow-up prenatal ultrasound examinations in the second and third trimester [54], the intrauterine growth retardation has been proved in the third trimester. Before the end of the second trimester the growth patterns of the biparietal and thorax diameter were inconspicuous [9].

If growth retardation occurs, the trunk of the fetus is earlier and more severely affected in about 70 per cent of the cases [9]. This is in accordance with the post-mortem findings of GRUENWALD [50], NAEYE and KELLY [77] and LARROCHE [68] that in SGA the liver – measured indirectly by thoracometry – is most affected compared to the brain which is affected to a lesser degree by fetal malnutrition.

4.1 Affected brain structures

Which are the major structural elements of the central nervous system susceptible to alteration by undernutrition?

Neurons: In the human the phase of neuroblast multiplication occurs at a more highly protected early period of gestation before the brain growth spurt begins – about the middle of gestation – [34]. Only particular regions of the cerebellum with the late-dividing granular neurons impinge on the growth spurt [37]. A deficit in cerebellar granule cells after undernutrition in the third trimester of pregnancy has been seen by several investigators. This may have consequences for future motor coordination and may be responsible for the "clumsy child" and some of the manifestations known as "minimal cerebral dysfunction". As a further effect from severe malnutrition is discussed a suppressed arborization of growing neurons and the impaired formation of synaptic boutons and terminals (the loci of most neurotransmitter molecules) [25].

Synapses: SHOEMAKER and BLOOM [92], using automated morphometric analyses of synapses by the electron microscope, report that both the frequency of synapses, as well as some staining properties can be modified by nutrition. According to DOBBING's [37] experimental work even quite moderate infant malnutrition during the

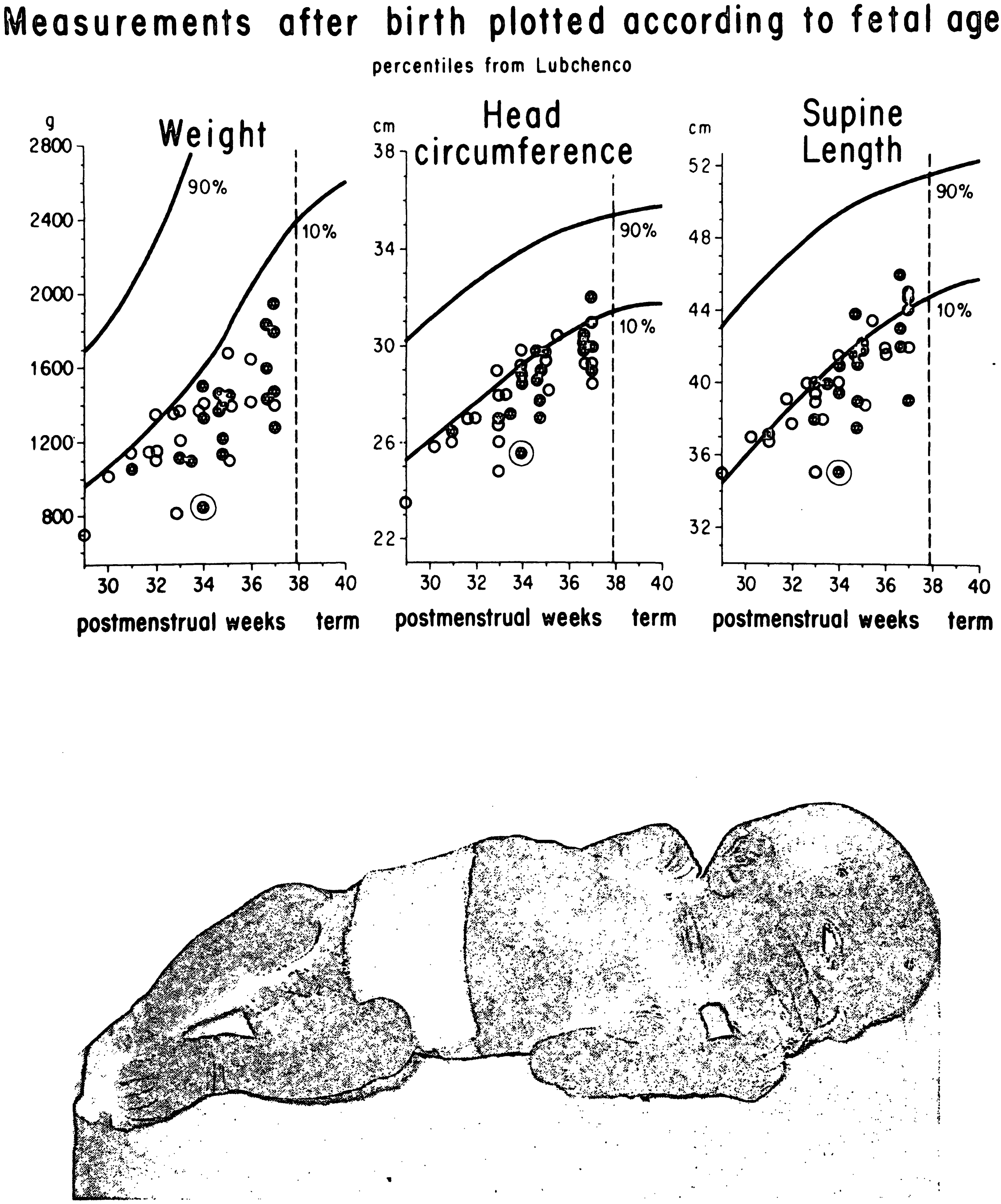


Fig. 6. Above: Weight, head circumference, and supine length after birth according to fetal age of 43 SGA preterm infants (circles) of the Bonn study [10], plotted on the intrauterine curves of LUBCHENCO [71, 72]. The circles with an asterisk signify infants with catch-up growth of head circumference. Below: SGA boy (case 2), the birth measurements (encircled) are reduced in all three parameters with the head least affected.

brain growth spurt period can reduce the number of synapses per neuron by up to 40 per cent. It is not yet known to what extent such deficits persist after restoring good nutrition. It is still unknown what the functional consequences may be of such a reduction in these presumably important structures. Although the morphological basis of higher mental function is still unknown, one could speculate that a deficit in synaptic connections provides a simple causal explanation for the relationship between undernutrition and intellectual impairment.

Neurotransmitters: Undernutrition might also affect the synthesis and the levels of the brain's most characteristic and probably most important constituents, the neurotransmitters [25].

Myelin: In a study of CHASE [23, 24], the total cerebroside-sulphatide content of brain stem-cerebrum analysed together was approximately 50% in infants with intrauterine undernutrition, compared with appropriately nourished infants. The ratio of cholesterol to cerebroside-sulphatide was used as an index of myelination. Because a very small percentage of myelin is present at birth, complete postnatal recovery should be possible with adequate postnatal nutrition.

4.2 Attempted evaluation of retarded brain growth

In Tab. III is demonstrated the relation between the reduction of head circumference and calculated brain weight [according to 36] in a group of 22 SGA infants without postnatal catch-up growth of head circumference, compared with the data of AGA preterm infants (n = 64) of the Bonn study [8] at expected date of delivery.

Tab. III. Difference between AGA and SGA preterm infants without catch-up growth in head circumference at expected date of delivery.*

	Head circumference mean, cm	Calculated brain weight mean, g
AGA preterm, n = 64	35.0	392.3
SGA preterm, n = 22	32.9	311.7
Difference	2.1 = 6% ($p < 0.0005$)	80.6 = 21% ($p < 0.0005$)

* p-values calculated by the t-test.

A growth retardation in head circumference of 2.1 cm (i.e., 6 per cent) in the SGA infants at expected date of delivery corresponds to a reduction in brain weight of 80.6 g (i.e., 21 per cent). Also at six months (corrected age) there still exists a highly significant difference in calculated brain weight of 108.5 g (i.e., 14 per cent), $p < 0.0005$, between these SGA and the AGA preterm infants.

Tab. IV shows growth relations in a group of SGA preterm infants with catch-up growth of head circumference, n = 22 [4, 9].

Tab. IV. SGA preterm infants with catch-up growth of head circumference: Effects on calculated brain weight.

	Difference between AGA and SGA	
Corrected age	Head circumference	Brain weight
36 postm. weeks	1.7 cm = 5% ($p < 0.0005$)	52.0 g = 18% ($p < 0.0005$)
40 postm. weeks	1.1 cm = 3% ($p < 0.0025$)	44.5 g = 11% ($p < 0.005$)
6 months	0.3 cm = 0.6% ($p > 0.1$)	28.0 g = 3% ($p > 0.1$)

A significant difference in mean head circumference of 1.7 cm (i.e., 5 per cent) at the age of 36 postmenstrual weeks, corresponding to a retardation in mean brain weight of 52 g (i.e., 18 per cent) $p < 0.0005$, is caught-up with until the age of six months. The remaining difference in head circumference of 0.3 cm, between both groups, corresponding to a reduction of brain weight of 28 g, is not significant anymore, $p > 0.1$. The SGA preterm infants with catch-up growth of head circumference also do not differ in their developmental quotients [48], and intelligence quotients [95] from AGA control infants [8, 89]. On the other hand, the test results of those SGA infants without catch-up growth of head circumference are significantly lower, $p < 0.0005$, compared to AGA control infants [8, 89].

4.3 Motor and mental development

Malnunitrion is still the most common cause of handicap, as stated by BAX [4]. In the developing world for example the most undernourished children are significantly more retarded than their somewhat better-fed age-mates, but here both nutritional and social factors appear to contribute to their backwardness [96]. BALAZS [2] has gained a thorough knowledge of the effects of early undernutrition from his animal experiments. He concludes, after reviewing the extensive literature, that human undernutrition affecting large communities in the world, is perhaps a very important non-genetic factor influencing the development of the central nervous system, and thus ultimately intellectual performance.

4.4 Hypoglycemia as an additional risk

Neonatal hypoglycemia in connection with intrauterine malnutrition and delayed as well as low-caloric postnatal feeding is considered disadvantageous for growth and development of the brain [22, 45, 51, 55, 84].

It has been known for long that a state of hypoglycemic shock, induced as a therapeutical measure in adults with mental disease, may heavily impair the brain and lead to dementia.

The majority of the SGA infants without catch-up growth of head circumference were born before 1971, at a time when regular controls of blood glucose were not yet common, and early and high-caloric feeding had not yet been introduced. It can be assumed that postnatal hypoglycemia has occured more often in these SGA infants without catch-up growth than in those SGA infants who were born after the introduction of regular controls of blood glucose and early and appropriate feeding.

Most of the SGA infants with catch-up growth were fed early and high-caloric [8, 99]. By this nutritional measure, the incidence and the detrimental effects of neonatal hypoglycemia were lowered too.

5 Incidence of hypoglycemia

According to CORNBLATH and SCHWARTZ [31], 'significant hypoglycemia in the neonate during the first week of life can be **defined** as whole blood glucose concentrations under 20 mg/100 ml (< 25 mg/100 ml serum or plasma) in the preterm or low birth-weight infant. Whole blood glucose values under 30 mg/100 ml (< 35 mg/100 ml serum or plasma) from birth to 72 hours of age and under 40 mg/100 ml (< 46 mg/100 ml serum or plasma) thereafter in the fullsized or term infant are significant low'. CORNBLATH [in 6] recommends at least two blood sugar determinations in order to exclude a possibly wrong estimate. But the second control must not lead to any delay in the prompt treatment of hypoglycemia. In males neonatal hypoglycemia is **more frequent** than in females [in 6]. The higher incidence of hypoglycemia in the male SGA infant may contribute to the higher perinatal death rate [20]. CORNBLATH [in 6] and REISNER [84] also point to a high occurence of hypoglycemia in the smaller of twins, weighing at least 25 per cent less than the larger twin. Infants can be hypoglycemic already at birth, without displaying any specific symptoms – which is often the case with very SGA infants – so that hypoglycemia is not recognized. BEISCHER [7] suggests that hypoglycemia is a significant cause of previously unexplained intrauterine deaths.

The incidence of hypoglycemia in preterm and full term SGA infants lies between 18 and 45 per cent [6, 21, 45, 70, 73, 83], Tab. V. FLUGE [45] reports a hypoglycemic rate of 15% in 323 newborn LBW infants.

In a study of 109 SGA infants from Toronto, born between 1974 and 1975, 15 per cent of the survivors did have hypoglycemia and of these infants, 73 per cent were damaged [26].

Tab. V. Incidence of hypoglycemia* in SGA infants.

Author	No. of infants	Incidence
RAIVIO and HALLMAN [83]	104 "Dysmature"	29%
BEARD et al. [6]	33 full term	18%
LUBCHENCO and BARD [73]	15 preterm 44 preterm	40% 21%
DE LEEUW and DE VRIES [70]	10 preterm 66 full term	45%
CALAME et al. [21]	73 preterm 100 full term	41% 41%
BRANDT	28 preterm ≤ 1500 g	43%

* Blood glucose concentration at least once 20 mg/100 ml or below.

5.1 Some results of the Bonn longitudinal study

In a group of 28 surviving SGA preterm infants of the Bonn longitudinal study with a birth weight ⩽ 1500 g, born between August 1971 and September 1978, hypoglycemia was observed in 43 per cent (n = 12), being without specific symptoms or asymptomatic in all cases except one. This was the case of an SGA boy (36 postmenstrual weeks, birthweight 1200 g) with neonatal convulsions who later developed a microcephalus, severe retardation, infantile spasms and cerebral palsy; but here additional risk factors were involved, above all a severe hypoxia, so that hypoglycemia alone cannot be considered etiological in this case. In the Stockholm study of ERIKSON and ZETTERSTRÖM [44] hypoglycemia was, next to hypoxia, the second most common cause for later handicap. Also, hypoglycemia as an additional symptom was found to be a bad prognostic sign in infants with other risk factors.

Two out of the eleven Bonn infants with asymptomatic hypoglycemia were born before early feeding was introduced, both now exhibit developmental retardation and one also has spastic hemiplegia. The remaining 9 infants of this group, all fed early and appropriately, develop within the normal range.

Blood glucose was estimated by the hexokinase method (Obstetric Department of the University Hospital Bonn, Director: Professor Dr. H. J. PLOTZ) or with the glucose oxidase method with the specific oxygen electrode using the Beckman-Glucose-Analyzer 2 (Children's Hospital of the University of Bonn, Director: Professor Dr. W. BURMEISTER).

In the following the risk of neonatal hypoglycemia in SGA infants shall be demonstrated in some case reports:

Case 1 (Fig. 7 above left, Figs. 8 and 9). A girl, born at 34 postmenstrual weeks by elective Cesarean section, birth weight 1130 g, supine length 37 cm, head circumference 27 cm. She is the first child of a 23-year-old woman, the pregnancy was complicated by gestosis with hypertension. At birth the blood glucose amounts only to 6 mg/100 ml, but the baby was asymptomatic. After an intravenous infusion of 10% glucose (80 ml/24 hours) and oral feed with adapted cow's milk, blood glucose rises within a few hours whereas the curve shows fluctuations as reported by other authors too [1, 41, 73, 86]. On the second day, the caloric intake amounts to more than 90 kcal/kg body weight and day (energy quotient, EQ), as shown in Fig. 8 below, and at the same time the infant starts to put on weight (Fig. 8 above). Inspite of this, there remains a tendency towards low blood sugar values (Fig. 7 above left). This could partially be explained by the very high needs of energy of the rapidly growing brain and the fast disappearance rate of glucose from the blood as has been reported again only recently by ROTH and GLADTKE [86]. This little girl, now six years old, has developed normally. She has now an IQ of 112 (STANFORD-BINET Intelligence Test). Fig. 9 below demonstrates the beautiful catch-up growth of head circumference following intrauterine growth retardation, documented by repeated ultrasound measurements (above) [9].

Case 2 (Fig. 7 above right, and photograph in Fig. 6 below). A boy, born at 34 postmenstrual weeks by elective Cesarean section, birth weight 850 g, supine length 35 cm, head circumference 25.5 cm. He is the second child of a 24-year-old mother after another VSGA infant of 700 g who died after birth. The pregnancy was uneventful, the mother smoked about five cigarettes a day. Immediately after birth is started an intravenous infusion of 10% glucose (80 ml/24 hours) and oral feed with adapted cow's milk, the energy quotient is 89 on the first day. Despite these measures there is a drop in blood glucose to 18 mg/100 ml at the age of four hours. Thereafter the blood glucose rises except one relaps to 19 mg/100 ml at the age of 21 hours (Fig. 7 above right). The full caloric intake of about 160 kcal/kg body weight and day is reached on the eighth day. The little boy, now seven years of age, has developed normally, and he has now an IQ of 100 (STANFORD-BINET Intelligence Test).

Case 3 (Fig. 7 below left) A girl, born at 33 postmenstrual weeks by elective Cesarean section, birthweight 1020 g, supine length 39 cm, head circumference 26 cm. She is the first child of a 36-year-old woman. The pregnancy was complicated by EPH gestosis. The baby did well after birth, the

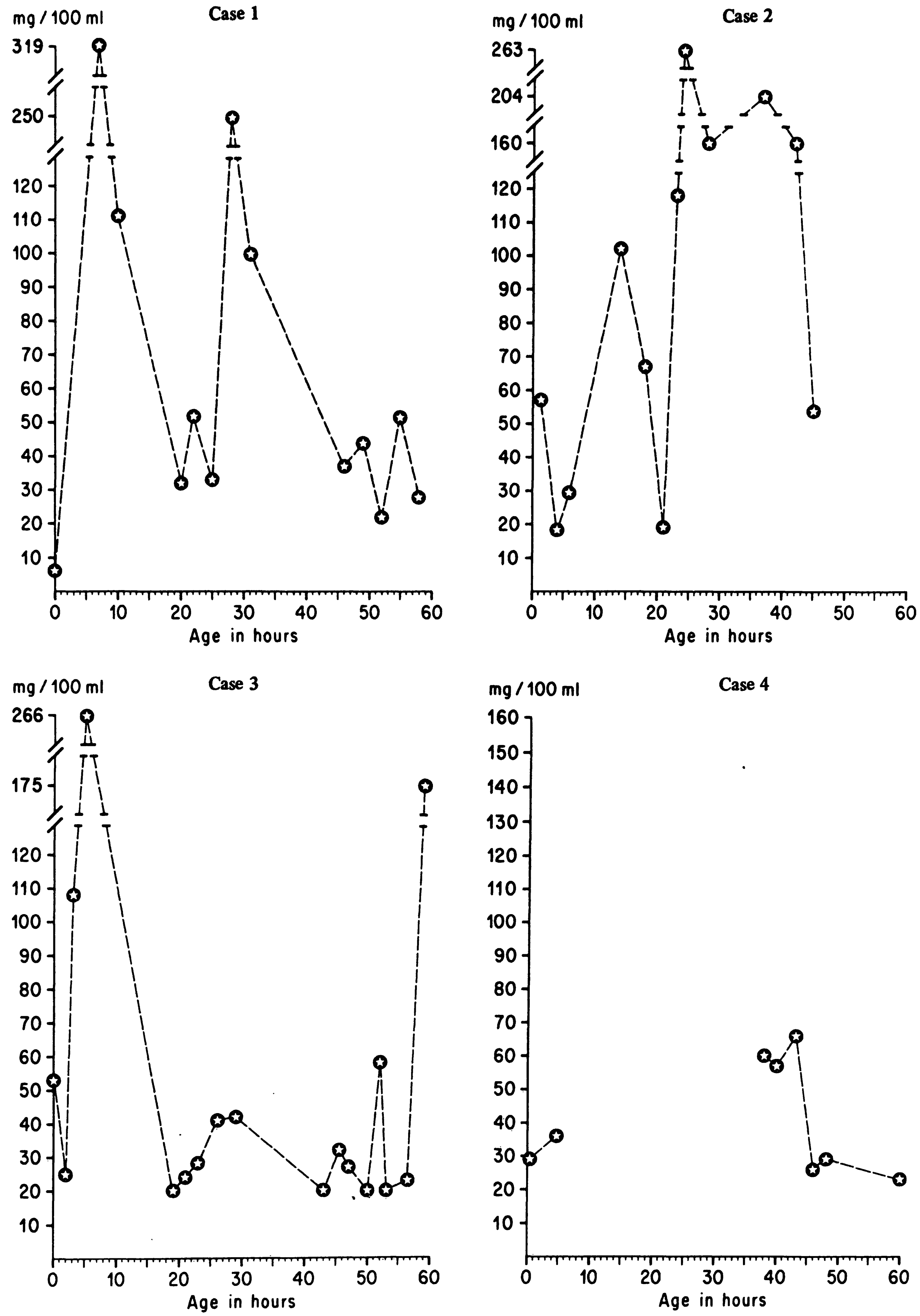


Fig. 7. Postnatal blood glucose concentrations in four SGA infants. For further comments see text.

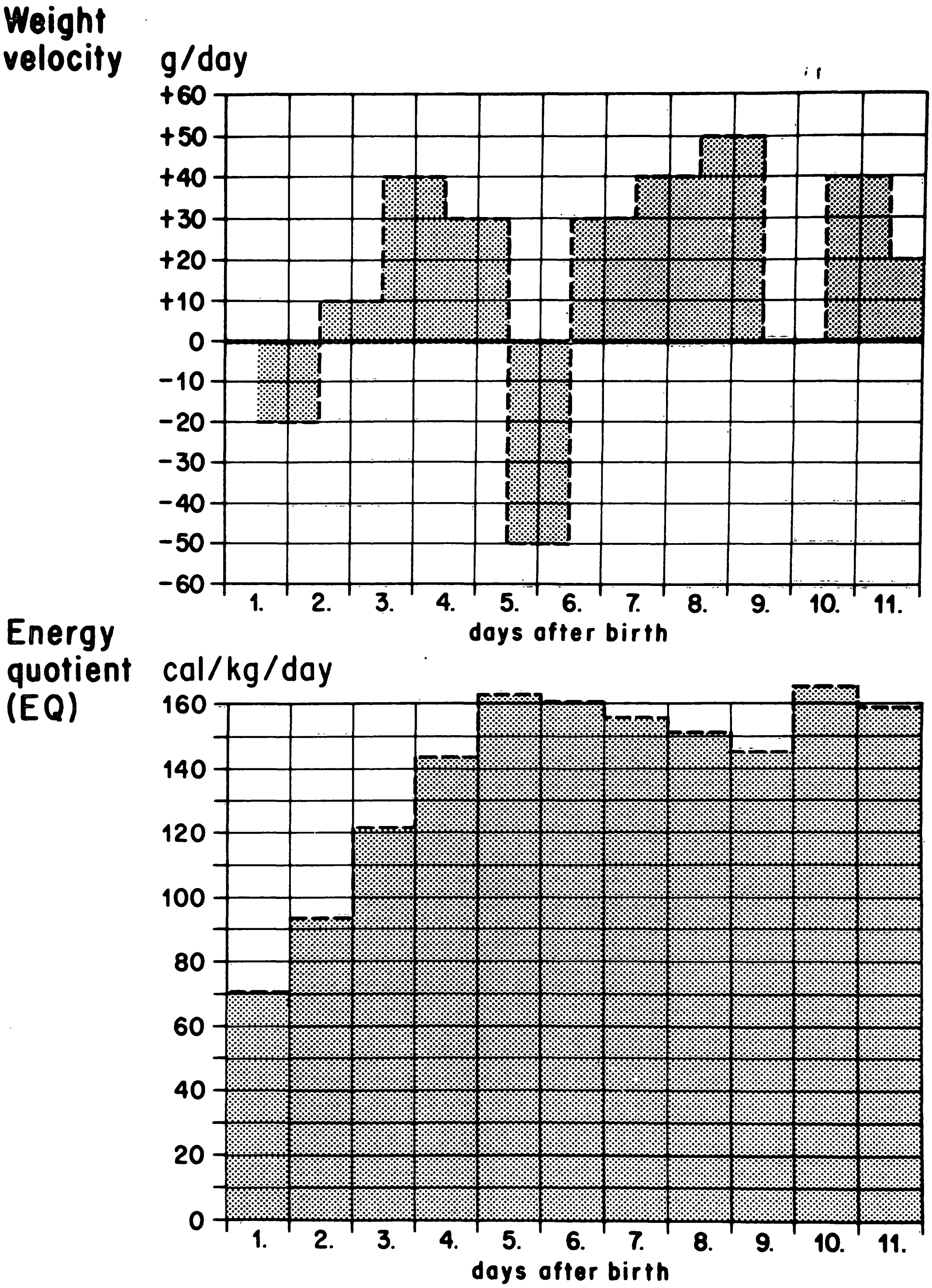


Fig. 8. Above: Weight velocity in g/day; below: caloric intake per kg body weight and day, the energy quotient, in a SGA preterm girl (case 1).

blood glucose at birth was 53 mg/100 ml; an intravenous infusion of 10% glucose was started and continued for 12 hours (altogether 35 ml). The infant was fed 3 ml cow's milk adapted to breast milk and 0.5 ml Dextro® neonat, an oligosaccharid solution, every two hours. At one hour of age the blood glucose dropped to 25 mg/100 ml. Thereafter, blood glucose levels rose. At 19 hours of age, blood glucose fell to 20 mg/100 ml and there remained a tendency towards low values until 50

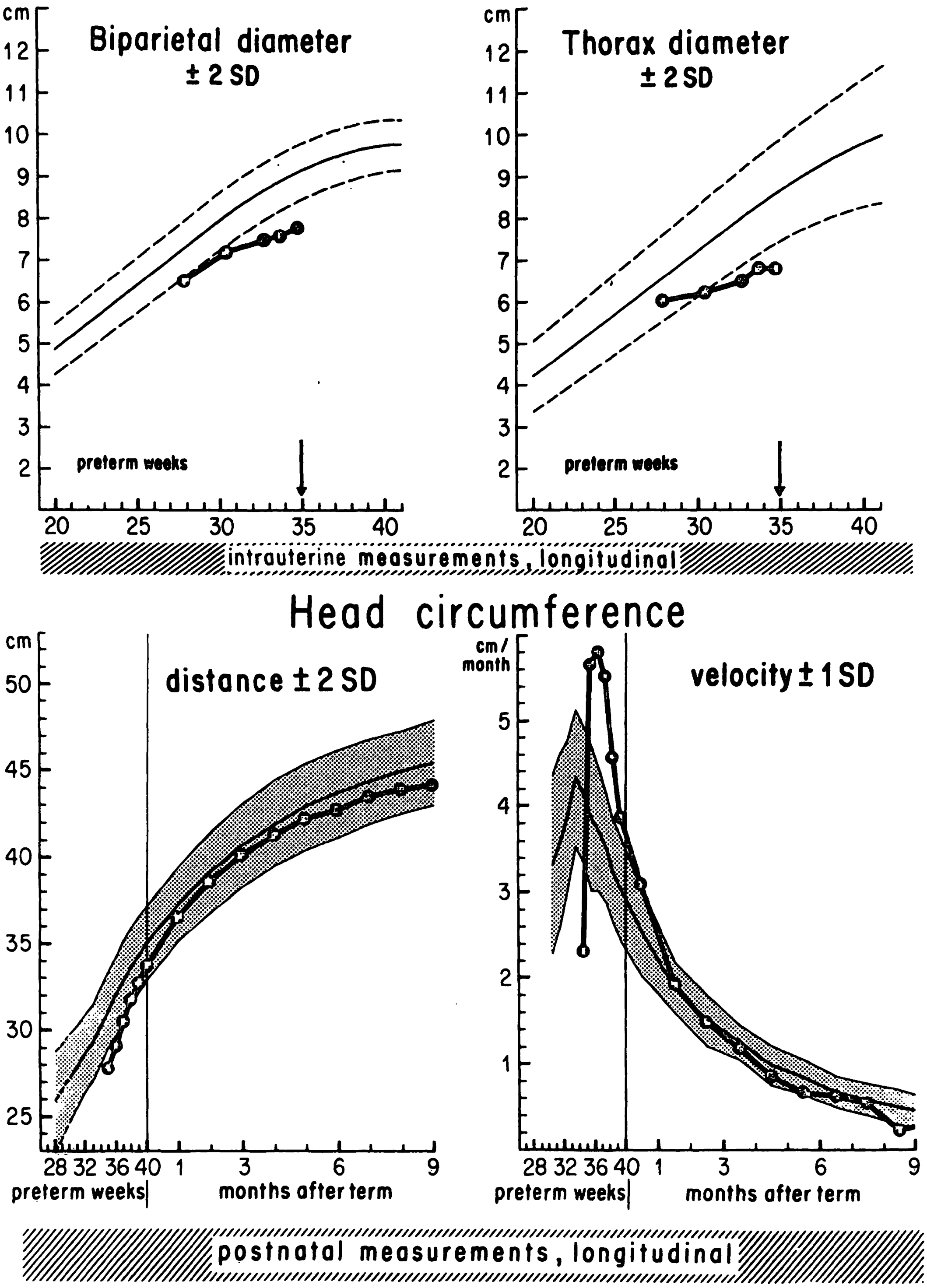


Fig. 9. Above: ultrasound measurements of intrauterine growth of biparietal and thorax diameter [9, 54]. Below: Postnatal measurements of head circumference, distance and velocity, plotted against the Bonn standards [10] of a SGA preterm girl (case 1).

hours of age; during this period, the infant was fed 5 ml adapted cow's milk every two hours and 0.5 ml Dextro® neonat, whereas the intravenous glucose was discontinued. In this case oral feeds seemed to be not sufficient to maintain adequate blood sugar levels. At 50 hours of age when the blood glucose again dropped to 20 mg/100 ml, the intravenous infusion of 10% glucose (80 ml/24 h) was restarted. A normal blood glucose level was thus maintained; the caloric intake reached 140 kcal/kg body weight and day at the age of four days. This little girl is now 4 years old and has developed normally. With appropriate feeding she exhibited catch-up growth: Her head circumference, being below the 10th percentile [72] at birth, corresponds now to the 50th percentile [11], similar to that of her younger sister, born at term. The height is in the range of the 25th percentile (13). Her mental development is above average (IQ 121, STANFORD-BINET Intelligence Test).

Case 4 (Fig. 7 below right). A boy, born at 38 postmenstrual weeks by elective Cesarean section, birth weight 1470 g, supine length 42 cm, head circumference 29.5 cm. He is the first child of a 25-year-old woman. The pregnancy was complicated by EPH gestosis. The infant did well after birth, the blood glucose being 29 mg/100 ml; an intravenous infusion of 10% glucose was started (120 ml/24 h), and the infant was fed immediately with an adapted cow's milk and Dextro® neonat. Despite the continuation of intravenous glucose and an energy quotient between 90 and 103, there was a tendency of low blood sugar values, i.e., 23 mg/100 ml at 60 hours and 24 mg/100 ml at 64 hours. In this case, regular follow-up examinations have not been possible. In the first year of life, the infant was fed inadequately on a diet of 250 g skimmed milk with a fat content of 1.5% as well as one fruit and one vegetable pap, both milk-free. By this the intrauterine growth retardation has not been caught up. At the age of three years, the head circumference is far below the third percentile [11]; the intelligence quotient (STANFORD-BINET Intelligence Test) amounts to about 90. Behavioral pecularities such as lack of concentration and cooperation as well as marked wilfulness, rendered the assessment difficult. This case exemplifies the effect which deficient postnatal nutrition might have in infants with prenatal malnutrition.

5.2 ROHRER index as indicator of hypoglycemic risk

$$\text{The ponderal index I} = \frac{100 \times \text{weight in g}}{(\text{supine length in cm})^3}$$

or weight-length ratio was introduced by ROHRER [85] for assessment of nutritional status and for comparisons among groups of infants. This index has also been used to judge the nutritional status of newborn infants [72, 75].

Between 30 and 40 postmenstrual weeks, the ROHRER index (50th percentile) increases from 2.33 to 2.62 [72], showing that the intrauterine fetus becomes heavier for his length during the last trimester of pregnancy. In SGA infants, the ROHRER index demonstrates clearly the growth retardation in weight and the risk of hypoglycemia because of the lack of energy reserves. Therefore a calculation of the ROHRER index is recommended in newborns with intrauterine malnutrition [12].

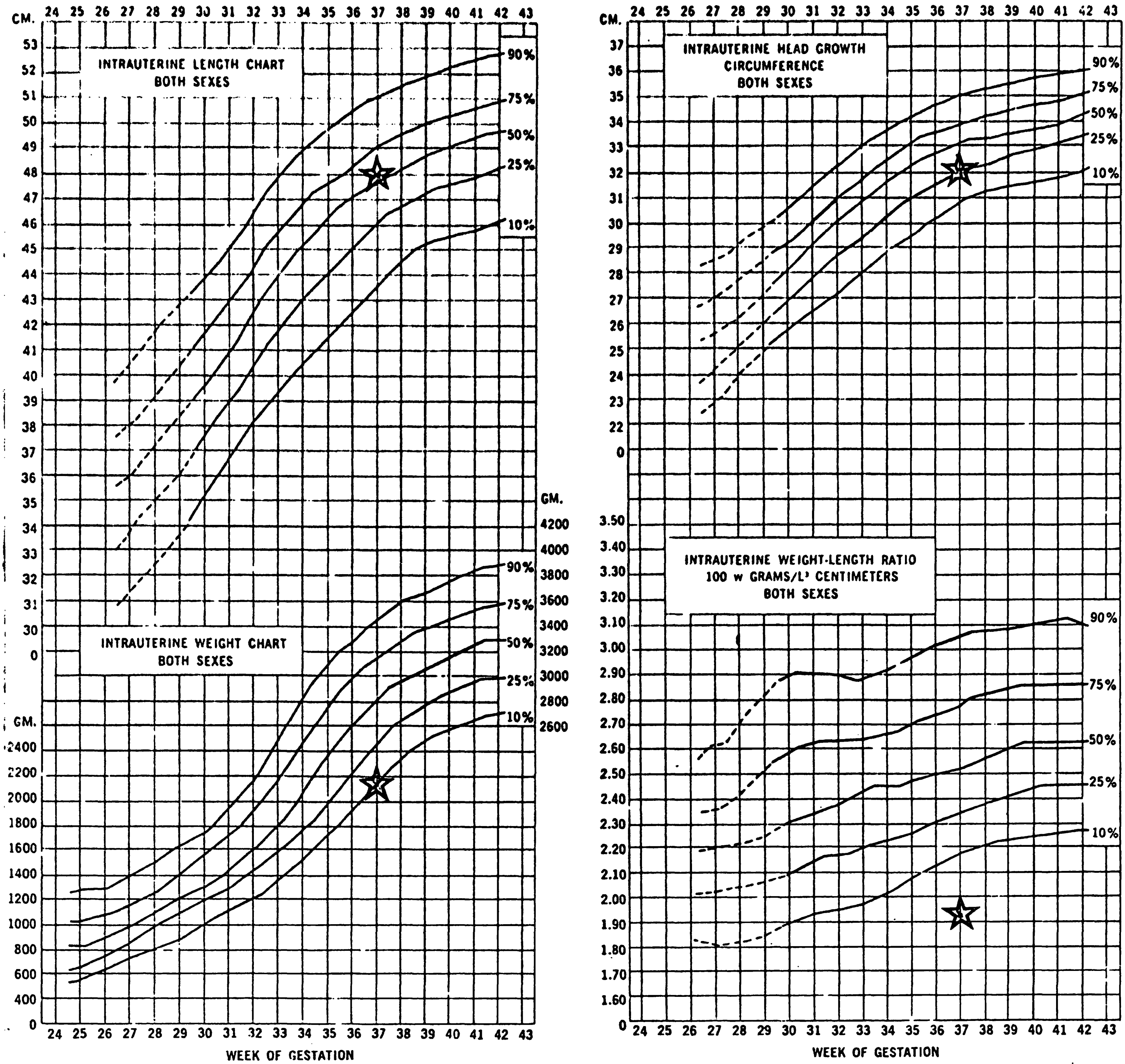
The next infant (case 5) with severe hypoglycemia, also typical in many aspects, is similar to a case, reported already 16 years ago by NELIGAN [78].

Case 5 (Tab. VI and Fig. 10). A boy, born by spontaneous vertex delivery at 37 postmenstrual weeks, birthweight 2230 g, supine length 48 cm, head circumference 32 cm. He is the second child of a 38-year-old woman, the pregnancy was normal. The mother smoked 10–20 cigarettes a day. The infant's condition at birth was good although he needed mask respiration for 1–2 minutes. At the age of 14 hours, the infant is transfered to the Bonn University Children's Hospital because of "postpartum asphyxia" (Tab. VI). The infant does well but is unusually quiet. Surprisingly, blood glucose is **0 mg/100 ml.** After immediate treatment (Tab. VI), blood

Tab. VI. Intrauterine growth retardation of a boy.

Admission at the age of 14 hours because of "postpartum asphyxia".
Until then no feeds, application of oxygen only.
Good overall condition, low motor activity, unusually quiet.

Blood glucose	on admission	0 mg/100 ml
	after 30 minutes	9 mg/100 ml
	after 90 minutes	137 mg/100 ml
Therapy	Dextro® neonat orally, 10% glucose infusion. Fed with adapted cow's milk. On first day energy quotient 88.	



From Lubchenco, L.O., et al.: Pediatrics 37:403, 1966.

Fig. 10. Intrauterine growth retardation of a boy (case 5), birth measurements, the asterisks, plotted against the intrauterine curves of LUBCHENCO [71, 72].

glucose rises to 9 mg/100 ml after 30 min, and to 137 mg/100 ml after 90 min. During the following days, blood glucose values stay within the normal range. The development of this boy, now two years old, is retarded markedly, developmental quotient (DQ) 72 [48], possibly due to a severe postnatal hypoglycemia of unknown duration. In this boy, the birth weight alone is not very suggestive, and neither is the length, if considered separately. The undernourished state of the infant and thus the risk of hypoglycemia become evident only after computing the ROHRER weight length index [85]. With a reduction to 1.94 (50th percentile 2.55), the ponderal index of this infant lies far below the 10th percentile of LUBCHENCO [72], see Fig. 10.

6 Possible pathogenetic mechanisms of neonatal hypoglycemia

Neonatal hypoglycemia is supported by both the lack of energy reserves and the very high needs of energy of the rapidly growing brain (Tab. VII).

The liver is struck most severely by intrauterine nutritional deprivation [56, 68], the ratio of brain weight to liver weight, normally 3:1 in the newborn [32], may be doubled in SGA infants up to 7:1 [1, 64]. This means that the brain utilizes glucose at a rate exceeding more than twice the glucose-producing capacity of the undersized liver. No substance normally present in the blood can replace glucose as a substrate for the brain's energy metabolism and the normal functioning of the CNS [94]. The disproportion between the weight of the brain and the liver in hypotrophic infants has been clearly demonstrated by LARROCHE [68] in relating organ weights to birth weight. From this follows that the brain weight lies more than 3 SD above the mean whereas the weight of the liver corresponds to the range of minus one SD. If gestational age is considered, both parameters are obviously below the mean with the liver much more affected than the brain (weight of the liver more than 3 SD below the mean versus that of the brain between minus one and minus two SD). The risk of hypoglycemia is also supported by the very low or lacking glycogen in the liver [91].

According to SINCLAIR and SILVERMAN [93] SGA infants are hypermetabolic in comparison to their AGA fellows of similar size which may further contribute to hypoglycemia.

Neonatal stress and anoxia cause an additional increase in glucose consumption, and here the levels of glucagon can rise up to the tenfold rate of normal values (8000 pg/100 ml) [65].

Ketone bodies, by-products of the metabolism of fatty acids, whose primary source is the liver [94], are often cited as a substitute source of energy; but **they are out of the question**, since fat reserves of SGA infants are very low or even not existent. An AGA preterm infant of 1000 g, e.g., has a store of fat of only 10 g [100]; in an SGA infant of similar weight the store is even less.

In none of the cases reported here the neonatal hypoglycemia has been preceded by beta-sympathomimetic tocolytic therapy. Only recently an increase in the incidence of neonatal hypoglycemia has been reported by SALING [88] and by EPSTEIN et al. [43] in the cases where the mothers were treated with beta-sympatho-mimetic drugs for inhibition of premature labor.

Tab. VII. Possible pathogenetic mechanisms of neonatal hypoglycemia in SGA infants.

1. Insufficient glycogen reserves of the liver [91].
2. Hypermetabolism [93].
3. Brain utilization of glucose exceeding glucose-producing capacity of the undersized liver [29].
4. Abnormally rapid disappearance of glucose from the blood [1, 86, 102].
5. Reduced or lacking fat reserves* [30].

* Total caloric deprivation in newborn pigs who have only 1% body fat at birth, leads to fatal hypoglycemia at the second or third day [30].

7 Clinical consequences

The precise nutritional requirements of very-low-birth-weight, especially SGA infants are still ill-defined. Caloric intake, much greater than in the healthy full term newborn, may be required in certain infants during the acute and recovery phase of illness and during catch-up growth.

The incidence of hypoglycemia up to 45 per cent in SGA infants or in infants with a disproportionate ratio of birthweight to length should alert pediatricians to the need for early and regular monitoring of blood sugar concentrations and for early oral and/or intravenous feeding of these newborns. Hypoglycemia, once diagnosed, should be treated as fast and as efficiently as possible, whether it presents with signs of glucose deprivation or not [18]. It is important to know that hypoglycemia may occur even under intravenous glucose in case the total caloric intake is lower than the mean resting metabolic rate which amounts in very low birth weight infants at least to 60 kcal [16, 29]. SGA infants are even more endangered because of their well-known hypermetabolism [93].
Early recognition and effective therapy with the prevention of convulsions may well lead to a better outcome than previously reported [31]. The state of hypoglycemia in the SGA infant will persist and worsen unless treated [73].
High-caloric feeding – if possible corresponding to the expected weight for the duration of gestation – should offer the SGA infant a chance of catch-up growth of head circumference, i.e., the chance of normal brain development.

8 Conclusions

8.1 Hypoglycemia

The importance of untreated neonatal hypoglycemia in infants with fetal malnutrition as risk factor for later neurological, motor and mental development is generally recognized. But the danger for the SGA infant to become hypoglycemic after birth is often underestimated in practice.
There may be several causes for this:
a) In some hospitals where blood glucose is regularly controlled, the infants are fed as soon as possible and therefore neonatal hypoglycemia occurs only rarely.
b) In other hospitals where blood glucose is controlled not regularly or never at all, hypoglycemia consequently cannot be found. Therefore prophylactic measures such as early and sufficient feeding of SGA infants will not be considered necessary.

8.2 Malnutrition

All studies of growth retardation or distortion of the brain following undernutrition in man and all experiments on undernourished animals leave only one conclusion: to feed infants appropriately and as soon as possible. With regard to this aspect, DOBBING (quoted by SHOEMAKER and BLOOM 92) asks whether all those efforts made in the numerous studies of brain distortion by undernutrition are still necessary. Future studies should focus on behavioral abnormality or other long ranged psychological consequences of undernutrition. Growth studies should also be stressed to learn more about the potential for a catch-up growth in relation to timing, duration and severity of undernutrition.

The computations were performed on the IBM/370-168 of the Regionales Hochschul-Rechenzentrum at the University of Bonn.

Keywords: Brain growth, catch-up growth, CNS-development, growth retardation, head circumference, intrauterine undernutrition, neonatal hypoglycemia, SGA preterm infants.

Zusammenfassung

Hirnwachstum, fetale Mangelernährung und klinische Konsequenzen
Fetale Mangelernährung ist immer noch eine der Hauptursachen für perinatale Mortalität und Morbidität. Das Vorkommen fetaler Mangelernährung ist konstant geblieben, das heißt, in unseren Industrieländern sind ein Drittel aller Kinder mit einem Geburtsgewicht unter 2500 g davon betroffen. In den Entwicklungsländern ist das Vorkommen beträchtlich höher. Intrauterine Wachstumsretardierung kann zusätzlich zum Gewicht auch die Länge und den Kopfumfang betreffen. Der Kopfumfang ist wegen seiner anerkannten Beziehung zur Hirngröße während der letzten Schwangerschaftswochen und im ersten Lebensjahr ein sehr wichtiger Wachstumsparameter. Eine kürzlich entwickelte Formel ermöglicht sogar die Berechnung des Hirngewichtes auf der Basis des Kopf-

umfanges. Bei Anwendung dieser Formel ergibt sich zwischen dem Alter von 32 postmenstruellen Wochen und 6 Monaten nach dem errechneten Geburtstermin eine Periode sehr schnellen Hirnwachstums, in der sich das Hirngewicht vervierfacht. Dieses enorme Wachstum ist ein wesentlicher Teil des allgemeinen Hirnwachstumsspurts. Die Vorgänge beim Hirnwachstumsspurt wie Gliazellvermehrung, Myelinisierung und Dendritenwachstum mit der Entwicklung des Dendritenbaumes sowie der synaptischen Verbindungen werden beschrieben und illustriert. Die Folgen pränataler Nahrungsdeprivation für das schnell wachsende Gehirn sind dabei abhängig von Zeitpunkt, Dauer und Schwere der Einschränkung. Im Gegensatz zu anderen Hirnstrukturen wird die Neuronenzahl von der meist erst im dritten Schwangerschaftstrimester beginnenden intrauterinen Mangelernährung nicht betroffen, weil sie bereits vollständig ist bevor der Hirnwachstumsspurt beginnt, etwa in der Mitte der Schwangerschaft. Mit modernen morphometrischen elektronenoptischen Analysen hat sich jedoch nachweisen lassen, daß bei früher kindlicher Mangelernährung die Anzahl der Synapsen pro Neuron bis um 40% reduziert sein kann. Mangelernährung beeinträchtigt ferner die Myelinbildung, die Zusammensetzung der Hirnlipide sowie die Menge der Neurotransmitter.
Bei Berechnung des Hirngewichts aus dem Kopfumfang ergibt sich, daß eine Retardierung des Kopfumfangswachstums zu einer entsprechenden Verminderung des Hirngewichts führt. Von den Mangelgeborenen der Bonner Studie hat die Gruppe mit postnatalem Aufholwachstum des Kopfumfanges ein normales Hirngewicht, berechnet anhand der Kopfumfangsdaten erreicht. In der anderen Gruppe Mangelgeborener ohne postnatales Aufholwachstum ergibt sich aus dem verminderten Kopfumfang eine entsprechende Verminderung im errechneten Hirngewicht.
Mangelernährung in einem frühen Alter wird als ein sehr wichtiger nicht-genetischer Faktor betrachtet, der die Entwicklung des Zentralnervensystems und damit letztlich die geistige Leistungsfähigkeit beeinflußt.
Wachstum und Entwicklung des Gehirns können weiterhin beeinträchtigt werden durch neonatale Hypoglykämie, die ein zusätzliches Risiko in der Gruppe der Mangelgeborenen darstellt. Neonatale Hypoglykämie ist definiert als Serumglukose-Konzentrationen unter 25 mg/100 ml bei Frühgeborenen und unter 35 mg/100 ml bei Reifgeborenen in der Zeit von der Geburt bis zum Alter von 3 Tagen. Bei männlichen Mangelgeborenen tritt eine neonatale Hypoglykämie häufiger auf, was möglicherweise zu deren höherer perinataler Mortalität und Morbidität beiträgt. Auch der kleinere Partner von Zwillingen wird häufiger von Hypoglykämie betroffen. Ein Kind kann schon bei der Geburt hypoglykämisch sein und braucht dabei keine spezifischen Symptome aufzuweisen. Hypoglykämie hat sich als für die Prognose ungünstiges Zeichen bei Kindern mit weiteren Risikofaktoren erwiesen, besonders, wenn sie nicht angemessen behandelt wird.
Die Hypoglykämie-Häufigkeit bei Mangelgeborenen (Früh- und Reifgeborene) liegt zwischen 18 und 45%. Hypoglykämie kann sogar während intravenöser Glukosegaben auftreten, wenn die Gesamtenergiezufuhr niedriger ist als die durchschnittliche Ruhestoffwechselrate. Die häufig als Ersatzenergiequelle angeführten Keton-Körper, Nebenprodukte des Fettsäurestoffwechsels, können diese Funktion nicht erfüllen, da die Fettreserven beim Mangelgeborenen extrem gering sind oder sogar ganz fehlen.
Das Vorkommen und der Verlauf der neonatalen Hypoglykämie wird an 5 Falldarstellungen von Mangelgeborenen der Bonner Longitudinalstudie beschrieben.
Wenn eine Hypoglykämie rechtzeitig entdeckt und behandelt wird, kann sie durchaus eine gute Prognose haben. Sofortige und energiereiche Ernährung des Mangelgeborenen, wenn möglich bei Berücksichtigung seines für die Schwangerschaftsdauer erwarteten Gewichts, soll das Kind vor einer schweren Hypoglykämie bewahren und ihm die Chance für ein Aufholwachstum des Kopfumfanges, d.h. Chance für eine normale Gehirnentwicklung bieten.

Schlüsselwörter: Aufholwachstum, Hirnwachstum, intrauterine Unterernährung, Kopfumfang, Mangelgeborenes, neonatale Hypoglykämie, Wachstumsretardierung, ZNS-Entwicklung.

Résumé

Croissance cérébrale, malnutrition foetale et conséquences cliniques

Malnutrition foetale est encore une des causes essentielles de la mortalité et morbidité périnatale. L'apparition de la malnutrition foetale est restée constante pendant les années passées, c'est-à-dire un tiers des enfants avec un poids au-dessous de 2500 g à la naissance en est affecté dans nos pays industrialisés. Dans les pays en voie de développement les taux sont considérablement plus hauts. Par un retard de la croissance intrautérine non seulement le poids mais aussi la taille et le périmètre crânien peuvent être affectés. A cause de sa relation reconnue avec le poids de cerveau pendant les dernières semaines de la grossesse et la première année le périmètre crânien est un paramètre de la croissance très important. Une formule même, développée recemment, rend possible la calculation du poids de cerveau, basée sur le périmètre crânien. En applicant cette formule il y en resulte une période de la croissance de cerveau très rapide entre l'age de 32 semaines postmenstruelles et 6 mois après terme, une période dans laquelle le poids de cerveau quadruple. Cet accroissement énorme est un part essentiel de «growth spurt» entiers du cerveau. Les éléments de «growth spurt» du cerveau (multiplication des cellules gliales, myélinisation, croissance des dendrites, c'est-à-dire le développement des arbres des dendrites et des contacts synaptiques) sont discutés et illustrés. Les effets de la déprivation de nourriture au cerveau, qui se développe très vite dépendent du moment du commencement, de la durée et de la gravité de la restriction. Les neurones – contrairement à les autres structures de cerveau – ne sont pas affectés numériquement de la malnutrition intrautérine, apparaissant le plus souvent pendant le troisième trimestre, parce qu'ils sont déjà complets

avant que le «growth spurt» commence, c'est au milieu de la grossesse. Analyses recentes au microscope électronique ont montrés qu'après une malnutrition infantile le taux des synapses par neurone peut être réduit jusqu'à 40%. Malnutrition de plus gêne la myélinisation ainsi que la composition des lipides de cerveau et la quantité des neurotransmitter différents.
En calculant le poids de cerveau du périmètre crânien il y résulte, qu'un retard de la croissance du périmètre crânien mène à un retard proportional du poids de cerveau. Entre les enfants hypotrophiques de l'étude longitudinale de Bonn un groupe avec «catch-up growth» de périmètre crânien postnatale arrive à un poids normale de cerveau, calculé des résultats du périmètre crânien. Dans l'autre groupe des enfants hypotrophiques sans «catch-up growth» postnatal résult du périmètre crânien diminuit une diminution du poids de cerveau correspondante. Malnutrition intrautérine et/ou pendant les premières mois est considérée comme un facteur non-héréditaire très important, influant le développement du système nerveux central et avec ça enfin la capacité intellectuelle.
Croissance et développment du cerveau peuvent être affectés en plus par l'hypoglycémie néonatale, qui représente un risque additionel pour les enfants hypotrophiques. Hypoglycémie est définie comme concentrations du glucose au serum au-dessous de 25 mg/100 ml chez les prématurés et au-dessous de 35 mg/100 ml chez les enfants nés à terme (dès la naissance jusqu'à l'age de trois jours). Chez les enfants hypotrophiques masculins l'hypoglycémie néonatale se trouve plus souvent; cela peut contribuer possiblement à leur mortalité et morbidité périnatale élevée. Egalement le plus petit membre des jumeaux est affecté plus souvent par l'hypoglycémie. Déjà à la naissance l'enfant peut être hypoglycémique et ça pas nécessairement avec des symptoms spécifiques. Hypoglycémie s'a prouvé un signe défavorable pronostique chez les enfants avec des autres facteurs de risque, particulièrement quand ils ne sont pas traités appropriément. La fréquence de l'hypoglycémie chez les enfants hypotrophiques (prématurés et nés à terme) se monte de 18 à 45%. Hypoglycémie peut apparaître même pendant l'application intraveineuse de la glucose, quand l'amenée de l'énergie totale est plus basse que la moyenne du métabolisme en repos. Des corps cétoniques, sous-produits du métabolisme des acides gras, souvent cités comme source d'énergie supplémentaire, ne peuvent pas remplir cette fonction parce que les dépôts de graisse sont extrêmement bas chez l'enfant hypotrophique ou même manquant entièrement. L'apparition et le cours de l'hypoglycémie néonatale chez les enfants hypotrophiques est discuté par cinq cas individuels de l'étude de Bonn.
Une hypoglycémie qui est découverte et traitée à temps peut avoir une prognose tout à fait bonne. Nourriture immédiate et riche en énergie, si possible correspondante à son poids de nouveau-né expecté pour la durée de la grossesse, protège l'enfant d'un hypoglycémie grave et lui offre la chance d'un «cacht-up growth» du périmètre crânien, et en même temps la chance d'un développement normal du cerveau.

Mots-clés:: «Catch-up growth», croissance cérébrale, dévéloppement du CNS, enfants hypotrophiques prématurés, hypoglycémie néonatale, malnutrition intrautérine, périmètre crânien, retard de la croissance.

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